# Electronically Modified Polymer-supported Cinchona Phase-transfer Catalysts for Asymmetric Synthesis of α-Alkyl-α-amino Acid Derivatives

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Merrifield resin-supported hydrocinchonidinium salts containing particular functional groups that can participate in hydrogen bonding were prepared and evaluated as chiral phase-transfer catalysts using the asymmetric benzylation of glycine imine ester. These electronically modified Merrifield resin-supported phase-transfer catalysts generally provided better enantioselectivities compared to the unmodified ones.

Cinchona alkaloid-derived quaternary ammonium salts have been frequently employed as chiral phase-transfer catalysts (PTCs) in the enantioselective phase-transfer catalytic alkylation of glycine imine ester such as **1** affording a variety of optically active natural and non-natural α-alkyl-α-amino acid derivatives.[1] In addition, considerable efforts have been made on the immobilization of cinchona PTCs on various polymer supports.[2] The most advantageous aspect to use a polymer-supported PTC (PS-PTC) is that it can be readily recoverable and recyclable, which makes PS-PTC more suitable for a large-scale production than unsupported PTCs from both practical and economical points of view (Chart 1).

Generally, natural cinchona alkaloids provide two sites for polymer attachment, thus cinchona PS-PTCs can be categorized into two types; type-1 PS-PTCs (O-supported PTCs) and type-2 PS-PTCs (N-supported PTCs). We have proposed that water molecule-mediated internal hydrogen bonding between C(9)-oxygen and special functional groups, such as 2′-F, 2′-C≡N, or 2′-$N^+$–$O^-$, in $N^+$(1)-arylmethyl moieties in cinchona PTCs plays a critical role for enhancement of enantioselectivity in the alkylation of **1**.[3a,3b] Based on this fact, we recently reported the design and preparation of a new class of type-1 cinchona PS-PTCs **3** in which hydrogen bonding inducing functional groups are incorporated in O-supported polymer part.[3c] As part of our ongoing studies towards the cinchona PS-PTCs, we herein report the design and preparation of electronically modified type-2 cinchona PS-PTCs **4b**–**4d** and **5b**–**5d**, and preliminary evaluation of their capabilities using asymmetric phase-transfer catalytic benzylation of **1**.

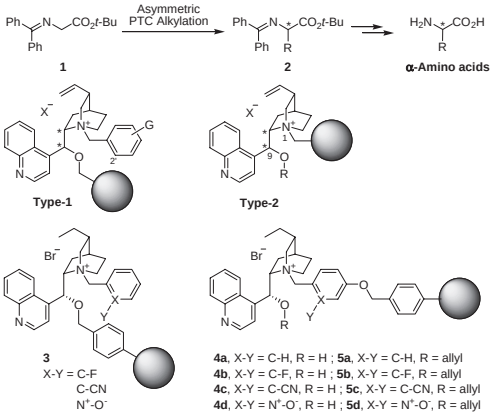
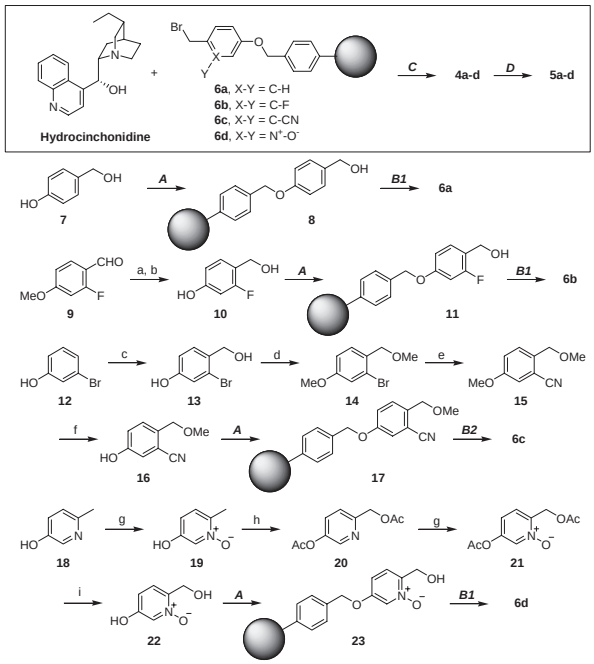


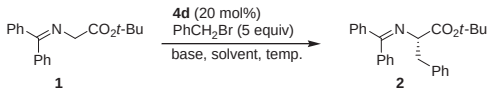

**Chart 1.**

Newly designed type-2 cinchona PS-PTCs **4b**–**4d** and **5b**–**5d** along with reference compounds **4a** and **5a** were prepared from (−)-hydrocinchonidine and the corresponding Merrifield




**Scheme 1.** *Reagents and Conditions*: (a) $BBr_3$, $CH_2Cl_2$, −78 °C to rt, 1 h, 86%; (b) $NaBH_4$, MeOH, rt, 10 min, 99%; (c) HCHO, 20% KOH, 60 °C, 6 h, 30%; (d) MeI, KOH, DMSO, rt, 30 min, 97%; (e) CuCN, DMF, reflux, 8 h, 80%; (f) NaSEt, DMF, reflux, 2 h, 60%; (g) *m*-CPBA, $CHCl_3$, rt, 4 h, 94% for **19**, 82% for **21**; (h) $Ac_2O$, reflux, 1 h, 90%; (i) 1 M HCl, acetone, reflux, 8 h, 76%; (***A***) Merrifield resin (Br, 0.94 mmol/g), $K_2CO_3$, DMF, reflux, 2 h, 96% for **8**, 93% for **11**, 94% for **17**, 96% for **23**; (***B1***) $Ph_3P$, $CBr_4$, $CH_2Cl_2$, 0 °C to rt, 24 h, 96% for **6a**, 88% for **6b**, 94% for **6d**; (***B2***) $BBr_3$, $CH_2Cl_2$, −78 °C to rt, 4 h, 99% for **6c**; (***C***) $CH_2Cl_2$, rt, 24 h, 92% for **4a** (0.59 mmol/g), 94% for **4b** (0.54 mmol/g), 93% for **4c** (0.57 mmol/g), 94% for **4d** (0.61 mmol/g); (***D***) allyl bromide, 50% KOH, $CH_2Cl_2$, rt, 24 h, 95% for **5a** (0.56 mmol/g), 99% for **5b** (0.54 mmol/g), 99% for **5c** (0.56 mmol/g), 99% for **5d** (0.59 mmol/g).

**Table 1.** Screening of reaction conditions




| Entry | Base[a] | Solvent[b] | Temp/°C | Time/h | Yield[c]/% | ee[d]/% |
|---|---|---|---|---|---|---|
| 1 | **A** | **E** | 0 | 12 | 48 | 69 |
| 2 | **B** | **F** | −50 | 6 | 0[e] | — |
| 3 | **C** | **E** | 0 | 44 | 90 | 86 |
| 4 | **C** | **F** | 0 | 36 | 89 | 83 |
| 5 | **C** | **G** | 0 | 24 | 92 | 90 |
| 6[f] | **C** | **G** | 0 | 40 | 92 | 89 |
| 7 | **D** | **G** | 0 | 120 | 75 | 85 |
| 8 | **C** | **G** | −20 | 60 | 87 | 90 |

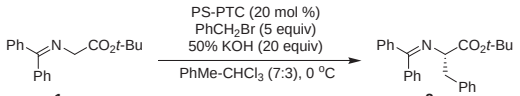
[a]**A**: 3.0 equiv of solid KOH; **B**: 3.0 equiv of solid $CsOH \cdot H_2O$; **C**: 20.0 equiv of 50% KOH; **D**: 20.0 equiv of 50% NaOH. [b]**E**: toluene; **F**: dichloromethane, **G**: toluene–chloroform (volume ratio = 7:3). [c]Isolated yield. [d]Enantiopurity was determined by HPLC analysis using a chiral column (Chiralcel OD-H) with hexanes/2-propanol as eluents, and absolute configuration of **2** obtained from all experiments was assigned as S by comparison of retention times of both enantiomers determined previously. [e]The imine moiety of the substrate **1** was hydrolyzed to afford benzophenone. [f]10 mol % of **4d** was used.

resin-bound benzylic bromides **6a**–**6d** as shown in Scheme 1. The benzyl bromides **6** were obtained by bromination of benzyl alcohol with $Ph_3P$–$CBr_4$ (for **8**, **11**, and **23**) or benzylic methoxy group with $BBr_3$ (for **17**). These Merrifield resin-supported precursors for bromination, **8**, **11**, **17**, and **23**, were prepared by O-alkylation of phenolic oxygen of **7**, **10**, **16**, and **22** with bromo-Merrifield resin, respectively. Compound **7** was commercially available, and 2-fluoro-intermediate **10** was obtained by two-step sequence, demethylation and reduction, started from 2-fluoro-4-methoxybenzaldehyde (**9**). For the preparation of 2-cyano-intermediate **16**, 3-bromophenol (**12**) was used as a starting material which was treated with formaldehyde in 20% KOH to afford hydroxymethylated compound **13**, followed by protection of two hydroxys with methyl groups. Converting bromide to cyanide with copper cyanide, and subsequent selective demethylation of the phenolic methoxy group with sodium ethanethiolate afforded **16**. The 2-*N*-oxide intermediate **22** was prepared by four-step sequence from 5-hydroxy-2-methylpyridine (**18**). **18** was first treated with 3-chloroperbenzoic acid (*m*-CPBA) to give *N*-oxide **19** which was then transformed to diacetoxypyridine compound **20** by acetic anhydride treatment. Oxidation of pyridyl nitrogen with *m*-CPBA followed by hydrolysis of two acetoxy groups gave **22**.

The catalytic efficiency of the newly prepared PS-PTCs was evaluated by catalytic asymmetric benzylation of **1** under the phase-transfer conditions. As there are some factors influencing enantioselectivity, such as catalyst, base, solvent, and reaction temperature, we performed this reaction with PTC **4d** under different conditions as described in Table 1. 50% KOH base provided the highest enantioselectivity and good chemical yield in proper reaction time compared to other bases. It was also found that both a mixed solvent of toluene–chloroform (7:3) and 0 °C of reaction temperature gave better results than others.

We next investigated the effect of the nature of catalyst on the reaction under the optimal conditions (Entry 5 in Table 1). As demonstrated in Table 2, all of the hydrogen bonding inducing functional group incorporated catalysts, **4b**–**4d** and **5b**–**5d**, showed enhanced enantioselectivities compared to the reference

**Table 2.** Catalytic enantioselective phase-transfer benzylation




| Entry | PS-PTC | Time/h | Yield/%[a] | ee/%[b] |
|---|---|---|---|---|
| 1 | **4a** | 26 | 89 | 80 |
| 2 | **4b** | 28 | 89 | 84 |
| 3 | **4c** | 26 | 88 | 88 |
| 4 | **4d** | 24 | 92 | 90 |
| 5 | **5a** | 24 | 90 | 78 |
| 6 | **5b** | 26 | 92 | 82 |
| 7 | **5c** | 20 | 88 | 91 |
| 8 | **5d** | 24 | 89 | 89 |

[a]Isolated yield. [b]Enantiopurity was determined by HPLC analysis using a chiral column (Chiralcel OD-H) with hexanes/2-propanol as eluents, and absolute configuration of **2** was assigned as S.

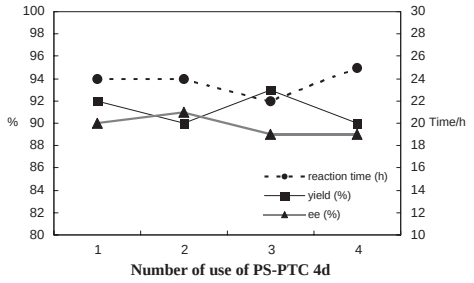



**Figure 1.**

catalysts, **4a** and **5a**.

The examination of the reusability of PS-PTC was then carried out with **4d** under the same conditions used in Table 2 (Figure 1). PS-PTS **4d** was recovered after the first benzylation, and the recovered **4d** was then employed in the second benzylation. No significant change was found in both chemical yield and enantioselectivity, and this tendency was continued in the additional two cycles.

In summary, we developed a series of new cinchona PS-PTCs in which hydrogen bonding inducing functional group is incorporated. All of the newly prepared PS-PTCs were found to have an ability to catalyze the asymmetric alkylation of **1** under phase-transfer conditions in good chemical/optical yields.

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